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Family With Autosomal Dominant Hidrotic Ectodermal Dysplasia: A Previously Unrecognised Syndrome?

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We describe a three-generation family with an autosomal dominant hidrotic ectodermal dysplasia consisting mainly of tricho- and onychodysplasia. One of the patients had supraventricular tachycardia, another had palpitations, and two others had sinus brachycardia. We consider that the clinical manifestations in this family differ significantly from those of the Clouston syndrome (their previous diagnosis) and places them in Group A, subgroup 1–3 (tricho-onychic) of the ectodermal dysplasia classification proposed by Freire-Maia and Pinheiro [1988, "Ectodermal Dysplasias"].

KEY WORDS: autosomal dominant inheritance, hidrotic ectodermal dysplasia, cardiac arrhythmia, sinus brachycardia

INTRODUCTION

The ectodermal dysplasias (EDs) comprise a group of >150 sporadic or hereditary disorders characterised by developmental deficiencies of tissues of ectodermal origin [Freire-Maia, 1971; Freire-Maia and Pinheiro, 1988; Pinheiro and Freire-Maia, 1994]. Freire-Maia [1971, 1977] proposed a classification for the EDs that included two groups. Group A was subdivided into sets that included at least two of the four cardinal ectodermal signs, namely, trichodysplasia (1), dental anomalies (2), onychodysplasia (3), and dyshidrosis (4). Group B included at least one of these signs plus at least one other ectodermal manifestation. Both groups could include anomalies of nonectodermal origin.

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Hidrotic ectodermal dysplasia, or Clouston syndrome, is an uncommon autosomal dominant genodermatosis, characterised by, among other signs, dystrophy of the nails, hyperkeratosis of the palms and soles, hypotrichosis, and presently categorised according to Freire-Maia in Group A, subgroup 1–2–3 [Clouston, 1929; Rajagopalan and Tay, 1977; Freire-Maia and Pinheiro, 1988]. We report on a family with a form of hidrotic ectodermal dysplasia appearing in three consecutive generations, which we consider to be an entity separate from Clouston syndrome and categorised in Group A, subgroup 1–3 [Freire-Maia, 1977].

CLINICAL REPORTS

Family History

The patients were white South Africans of Afrikaans origin (Fig. 1).

Patient 1 (III-6)

The proposita, a 13-year-old girl, presented to a cardiologist (SF) for assessment of episodes of palpitations and syncope. At birth she had been noted to have no hair. By age 3 months she had developed sparse, thin scalp hair and her nails were noted to be abnormal. Primary and secondary tooth eruption and development were normal. She was an otherwise healthy child, engaging in normal childhood activities, including sports, despite living in a hot climatic area. Her sweating was considered normal, and she had not experienced any episodes of hyperthermia associated with activity or illness.

She was well grown, with weight of 44 kg (just below the 50th centile), height 157 cm (50th centile), and in early puberty. Breast development was between Tanner stages I and II and her nipples appeared normal. She had relatively short, thin, sparse, pale scalp hair, which was more notably affected at the front and sides of her head (Fig. 2). Eyebrows were absent, eyelashes were short, thin and sparse, there was almost no hair in her axillae and pubic area, and limb hair was absent. She had no palmoplantar keratoderma and her skin was otherwise normal. Teeth were normal and she had minimal caries. The fingernails were dystrophic, thickened, more concave than normal with the distal half of the nail not being attached to the nail bed, resulting in

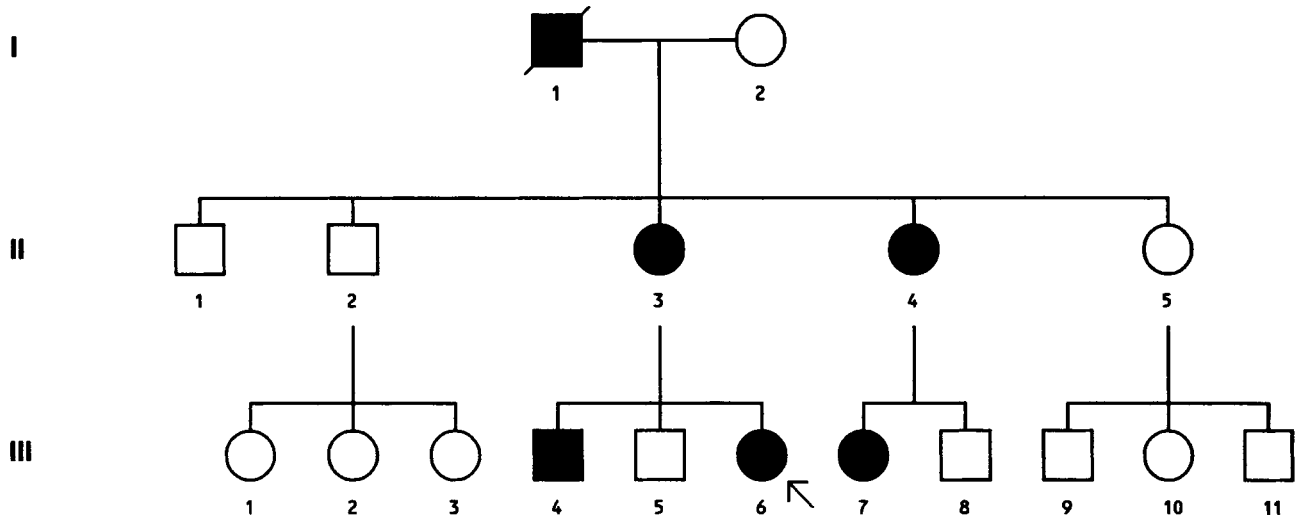

Fig. 1. Pedigree.

a gap between the centre of the free edge and the nail bed. They were not brittle and with care could be grown to normal length. The toenails were dystrophic, but not lifted from the nail bed. Examination of the cardiovascular system (CVS) was essentially normal. Blood pressure was 110/70, mm Hg and pulse 72/min, with a regular rhythm.

An electrocardiogram (ECG) taken previously during an episode of palpitations had recorded a pattern of supraventricular tachycardia. However, a resting ECG, taken during the cardiovascular evaluation, showed a rate of 75/min with sinus rhythm and a PR interval of 0.12 seconds, which is at the upper limit of normal for age. Chest roentgenogram and cardiac ultrasonography findings were normal. Skull and hands roentgenograms were normal, with no thickening of the calvara or tufting of the distal phalanges. Thyroid function tests were normal. The episodes of supraventricular tachycardia were controlled successfully with Verapamil.

Patient 2 (III-4)

A 20-year-old man, the brother of the proposita (III-6), had hair on his head from birth, but it was always sparse, especially on the sides and front. From infancy his nails were abnormal, but he sweated normally, had had normal primary and secondary dentition, and had proceeded normally through puberty. He shaved daily. He participated actively in sporting activities and had no symptoms related to hyperthermia or the CVS.

Clinical examination revealed an athletically built young man, with weight of 78 kg (>75th centile) and height 174 cm (below 50th centile). His scalp was well covered with hair of normal length and appearance, except on the front and sides of his head, where it was thinner, lighter in colour, and sparser (Fig. 3). His

Fig. 2. Face of Patient 1 (III-6). Note alopecia and absent eyebrows.

Fig. 3. Lateral view of head of Patient 2 (III-4). Note thinning and lighter colour of the hair on the side of the head.

beard was palpably normal, the hair on his arms fine, and the axillary and pubic hair had a normal distribution, but was fine and sparse. The medial third of his eyebrows were normal, the rest sparse, and he had normal eyelashes. His skin, including the palms and soles, was normal and his teeth were well aligned, healthy, and had minimal caries. Fingernails (Fig. 4) and toenails were identical to those of his sister (III-6). He had a blood pressure of 140/90, mm Hg a normal volume, regular pulse of 44 beats/min, and no cardiac murmurs.

The ECG recorded a rate of 46 per minute, sinus rhythm, but with a PR interval of 0.16 seconds. The pattern was one of a sinus brachycardia. Cardiac ultrasonography findings were normal. Chest, skull, and hand roentgenograms were normal.

Patient 3 (II-3)

The mother of patients III-4 and III-6 was a 40-year-old woman born without scalp hair, and her hair never grew well. Although she had eyelashes, her eyebrows and the hair on her limbs did not grow. She sweated normally, but complained of excess sweating under her wig and from her feet in hot weather. Her nails had been abnormal from birth, and until she had grown them long, they were identical to her daughter's and son's nails (Patients III-4 and III-6). She had no CVS symptoms.

On examination she was short, 151 cm (3rd centile), and overweight 78 kg (90th centile). She had minimal short, very fine, scalp hair, no eyebrows, short sparse eyelashes (Fig. 5), no hair on her limbs, and very fine, sparse lanugo type hair in the axillae and pubic area. Her skin, including the palms and soles of the feet and her teeth were normal, but her fingernails, although dysplastic, had been allowed to grow beyond the tips of the fingers and did not obviously appear to have "lifted" from the nail bed (Fig. 6). The toenails were small and dysplastic. Cardiovascular examination documented a regular pulse of 50/min, blood pressure of 160/70, mm Hg, and no cardiomegaly or murmurs.

The ECG had a rate of 48 per minute, sinus rhythm, and a PR interval of 0.20 seconds, indicative of sinus brachycardia. Cardiac ultrasonography was normal. Chest, skull, and hand roentgenograms were normal. A skin biopsy of her scalp, performed 10 years previously, confirmed the presence of hair follicles, with normal hair shafts, normal sweat and sebaceous glands, and a thin dermis.

Fig. 5. Face of Patient 3 (II-3). Note minimal short, fine scalp hair, and no eyebrows.

Patient 4 (I-1)

The father of patients II-3 and II-4 was the first person in the family known to be affected with the condition. His daughters recollected that he had sparse scalp hair, no hair on his limbs, sweated normally, and had thick nails like theirs. He allegedly had been a healthy individual until three months prior to his death, which was due to cardiac failure.

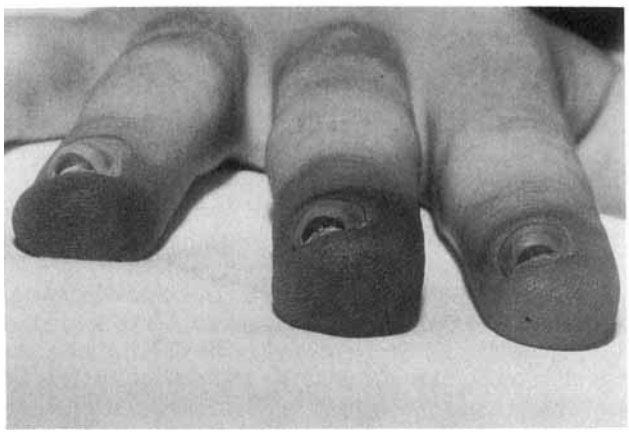

Fig. 4. Fingernails of Patient 2 (III-4). Note thickening and tunnel like gap between nail and nail bed.

Fig. 6. Fingernails of Patient 3 (II-3). Note nails are dysplastic and have grown beyond the fingertip, obliterating the gap between nail and nail bed.

Patient 5 (II-4)

Unlike her sister (II-3), this patient had hair from birth, which grew to a reasonable length but fine and patchy. Her eyebrows did not grow, but her eyelashes were normal. Nails were abnormal from infancy, but her teeth and skin were normal and she sweated normally.

On questioning she admitted to intermittent palpitations over a period of several years. She had not sought medical advice for these. Previously she had had a thyroidectomy for a goitre.

She was a short, slightly obese woman, whose hair was fine. Over the side of her head it appeared thicker, but was very sparse over the occiput and frontal areas. She had no eyebrows, short sparse eyelashes, no limb hair, fine sparse hair in the axillae, but her pubic hair was thicker and more dense than all the other affected female individuals and had a normal distribution.

Her fingernails were well manicured and long, having been grown to the extent that they curved over the end of the fingers. However, they were dysplastic and concave. Teeth, skin, including palms and soles, and CVS were normal, although as she refused assessment by a cardiologist, a full cardiac investigation was not undertaken.

Patient 6 (III-7)

This daughter of Patient II-4 was born with sparse scalp hair, had never developed eyebrows or limb hair, but had eyelashes and normal teeth. Her nails were abnormal from infancy. She sweated normally and had no CVS symptoms.

She was a well-grown 19-year-old woman, with fine sparse scalp hair, no eyebrows, short sparse eyelashes, and thick, normally distributed genital hair. Her axillae were shaved, her teeth and skin, including palms and soles, were normal, and her nails, which were manicured, appeared almost normal. However, she had lost the nail from her left thumb, and the excessive overgrowth of the proximal nail bed, which lifted the nail from the bed, was apparent (Fig. 7). She recently underwent a full cardiological assessment and her CVS was found to be normal on clinical, ECG, and ultrasound examination.

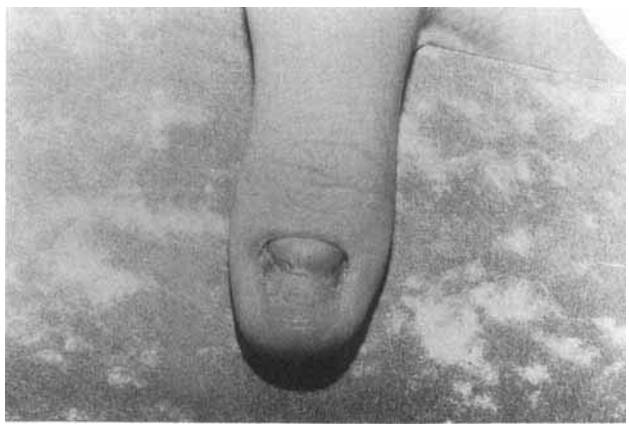

Fig. 7. Thumb of Patient 6 (III-7). Note overgrowth of tissue in proximal third of nail bed.

DISCUSSION

The EDs are a large heterogeneous group of conditions, which were formerly subdivided into hidrotic and anhidrotic forms. The hidrotic form, in which affected individuals perspired freely, was typified by Clouston syndrome. This is an autosomal dominant genodermatosis, characterised by nail dystrophy, keratoderma of palms and soles, skin pigmentation of knuckles, axillae, elbows, areolae, pubes, and ischial tuberosities, and hypotrichosis. The hypotrichosis includes variable alopecia, loss or thinning of the eyebrows, especially in the lateral two-thirds, sparse, short eyelashes, and reduced or absent body hair. Axillary and pubic hair varies from almost normal to thin and sparse, but with a normal distribution [Clouston, 1929; Wilkey and Stevenson, 1945; Rajagopalan and Tay, 1977].

Onychodysplasia in Clouston syndrome has been described as appearing in three types: small cone-shape or triangular nails, nails of normal size with a moderately thickened plate but with nail surface evidence of dystrophy (grooves, pits, ridges, longitudinal striation and chips of the edges and sides), and smaller thickened, less convex (more concave) in shape with the distal half of the plates separated from the nail bed [Clouston, 1929; Rajagopalan and Tay, 1977].

Freire-Maia and Pinheiro, in their 1984 review of EDs, argued that Clouston syndrome could exhibit dental anomalies, and it was thus classified in Group A, subgroup 1-2-3. However, dental anomalies are not essential for the diagnosis to be considered. Clouston [1929], on roentgenogram examination of his cases, noted thickening of the calvara and marked tufting of the bones of the terminal phalanges.

The individuals we have reported here were initially diagnosed as having Clouston syndrome, presumably on the basis of the autosomal dominant pattern of inheritance, the trichodysplasia, and the onychodysplasia. However, none of the affected individuals examined had keratoderma of the palms and soles or skin pigmentation. They all had well-formed, perfectly aligned, healthy teeth, with notably few caries. The trichodysplasia documented in this family was comparable of that described in Clouston syndrome and exhibited marked intrafamilial variability, with males less affected than females. The onychodysplasia present in all the patients described was uniform and in all the cases was similar to the third form of dystrophy described above. However, varying nail care had resulted in a differing appearance of the fingernails between relatives.

Roentgenograms of the skull and hands of three of the patients (II-3, III-4, III-6) did not exhibit the thickening of the calvara and tufting of the distal phalanges described by Clouston [1929].

Four of the patients (II-3, III-4, III-6, III-7) had full cardiological examination. This was undertaken since the proposita (III-6) presented with palpitations and was diagnosed and successfully treated for episodes of supraventricular tachycardia. Two patients (II-3 and III-4) on clinical examination had relative brachycardia. Patient II-4 had also experienced palpitations. The ECG examination of patients II-3 and III-4 indicated

TABLE I. Clinical Findings Documented in the Patients (III-6, III-4, II-3, I-2, II-4, III-7) and in Clouston Syndrome

Clinical findings	Clouston syndrome	Patient 1 III-6	Patient 2 III-4	Patient 3 II-3	Patient 4 I-1	Patient 5 II-4	Patient 6 III-7
Autosomal dominant inheritance	+	+	+	+	+	+	+
Trichodysplasia	+	+	+	+	+	+	+
Onychodysplasia	+	+	+	+	+	+	+
Dental anomalies	+	–	–	–	?	–	–
Dyshydrosis	–	–	–	–	–	–	–
Skin:							
hyperkeratosis	+	–	–	–	?	–	–
hyperpigmentation	+	–	–	–	?	–	–
Skeleton:							
thickened calvara	+	–	–	–	?	?	?
tufted terminal phalanges	+	–	–	–	?	?	?
Cardiovascular system:							
palpitations	–	+	–	–	?	+	–
arrhythmia	–	+	–	–	?	–	–
sinus brachycardia	–	–	+	+	?	?	–

they had sinus brachycardia. No evidence of other cardiological abnormalities, including cardiomyopathy, was noted in the four patients who underwent full cardiological assessment. The association of ED and cardiac arrhythmias is, to the authors' knowledge, rare, but was previously reported in association with dilated cardiomyopathy [Hammil et al., 1988]. The three cases reported were all children, but their sudden development of cardiomyopathy and arrhythmias raises the possibility that the rapid development of cardiac failure and subsequent death of patient I-1, may have been due to cardiomyopathy. Cardiac arrhythmias and sinus brachycardia have not previously been documented in the families reported with Clouston syndrome [Clouston, 1929; Wilkey and Stevenson, 1945; Rajagopalan and Tay, 1977; Hammil et al., 1988]. Familial autosomal dominant sinus brachycardia has previously been documented [Sarachek and Leonard, 1972]. Thus in this family the sinus brachycardia, if dominantly inherited, may be due to an independent gene closely linked to the ectodermal dysplasia gene of this condition and thus segregating with it, or unlinked and segregating with this gene by chance. Alternately, we would propose that the cardiac arrhythmias exhibited in this family are a part of the syndrome and thus a clinical manifestation of the same gene.

Because of the differences noted above between Clouston syndrome and the patients we describe (Table I), we would propose that our patients have an autosomal dominant hidrotic ectodermal dysplasia that differs from Clouston syndrome, and according to the classification of Freire-Maia, should be in the tricho-onychic subgroup (1–3) of Group A [Freire-Maia, 1977]. The only other autosomal dominant condition in this subgroup, pili torti and onychodysplasia [Beare, 1952], can be distinguished from that of our patients by the postpubertal appearance of the trichodysplasia.

Joachim [1936] described a woman, of a six-generation French-Canadian family, who was considered to the present to have Clouston syndrome. She had trichodysplasia, and the onychodysplasia she exhibited was identical to that described in this family. No mention was noted in the case report of keratoderma, skin pigmentation, or abnormal teeth, but significantly she was reported to have palpitations, a symptom suffered by Patients III-6 and III-4.

It is possible that this case may previously have been incorrectly classified and could represent the first case of the condition described in the family we have reported.

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